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Commentary

A call from patient-researchers to advance research on long COVID

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Long COVID is a chronic and often disabling illness with long-term consequences. Although progress has been made in the clinical characterization of long COVID, no approved treatments exist and disconnects between patients and researchers threaten to hinder future progress. Incorporating patients as active collaborators in long COVID research can bridge the gap and accelerate progress toward treatments and cures.

The impact of long COVID

Despite proclamations of a "return to normal," COVID and long COVID continue to affect the health and well-being of people worldwide. The May 2024 Household Pulse Survey found that 6.0% of adults in the US currently had long COVID (95% confidence interval [CI]: 5.6–6.4). Of this group, 25.4% reported "significant activity limitations" due to long COVID (95% CI: 23.1–27.8). The incidence and burden of long COVID may be even higher in adults living in developing or low-income nations.[1] Children also suffer substantial morbidity from long COVID: a recent *Pediatrics* study estimated that up to 5.8 million children in the US are affected by long COVID.[2]

Long COVID cost the US economy approximately $3.7 trillion over the first five years of the pandemic alone, including $997 billion in lost income for those disabled by long COVID. Long COVID can persist months or years after infection with little recovery over time, and insights from other infection-associated chronic conditions and illnesses (IACCIs) suggest symptoms may be lifelong. The long-term prognosis for IACCIs can vary—while some people experience improvements, the illness can progressively worsen for others.

We are part of a cohort of patient-researchers taking on the challenge of developing the nascent field of long COVID research. The Patient-Led Research Collaborative (PLRC) is an international research and advocacy organization operated by people with long COVID. We are scientists, researchers, healthcare workers, community organizers, and other professionals who have long COVID or an associated condition and/or are caregivers for someone with the condition. PLRC authored the first report on long COVID, the first paper characterizing the 200+ symptoms of long COVID,[3] and a review that has been instrumental in guiding the field.[4] Since our founding, we have disbursed millions of dollars in grants to biomedical researchers, advocated for public funding for long COVID research, conducted many patient-led research studies, and collaborated with other research organizations and academic centers on long COVID publications. We ground our work in the principles of disability justice and participatory research methods and in the knowledge that those who experience an illness are best able to identify research questions and solutions.

Although significant strides have been made in defining long COVID symptomatology, prevalence, and impact, the quality and relevance of long COVID research varies and clinical trials of potential treatments have been slow. No US Food and Drug Administration (FDA)-approved treatments or preventatives for long COVID exist and as patients await evidence-based care, many engage in self-experimentation on the edges of medical science. Patients are frustrated with the lack of progress on treatments and diagnostics, with clinicians and researchers who psychologize long COVID and studies that are not accessible or do not investigate patient priorities. This Commentary recommends a path toward resolving disconnects between patients and researchers to improve long COVID research and the lives of people with the condition (Figure 1).

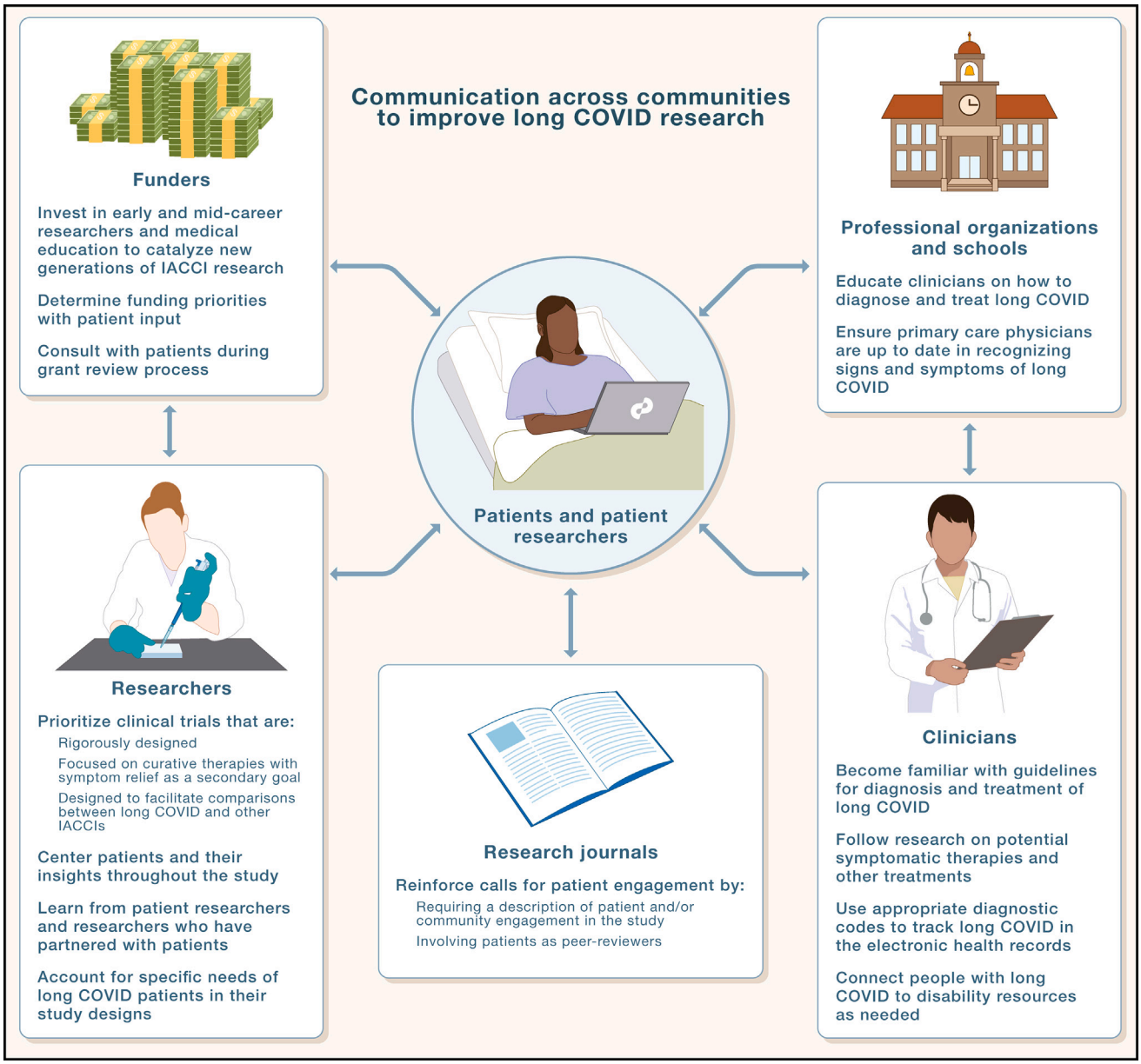

Figure 1. Improving long COVID research
This figure illustrates the communities involved in long COVID research and what steps should be taken to resolve disconnects in long COVID research. Communication between and across these groups is essential.

Patient contributions are key to long COVID research

Insights from patients

In the 4+ years since the condition was first formally identified, several promising research avenues on long COVID have emerged. IACCIs, including long COVID, develop following infections with pathogens and are characterized by chronic and often disabling symptoms that persist long after the acute phase of infection. Early in the pandemic, patients with other IACCIs highlighted similarities between long COVID and their conditions, calling for shared research and treatment agendas. Indeed, many people with long COVID meet the diagnostic criteria for myalgic encephalomyelitis (ME), an IACCI that can also be triggered by other infections. Some overlapping symptoms of ME and long COVID include orthostatic intolerance, cognitive dysfunction, fatigue, and post-exertional malaise (PEM). PEM refers to exacerbation of symptoms after physical, cognitive, or emotional exertion. Research on other IACCIs has accelerated insights into long COVID. For example, shared pathologies of long COVID and ME include immunological dysfunction, reduced cerebral blood flow, cerebral hypometabolism, and reactivation of latent viruses or infections.[4]

Contributions of patient-led research

One long-standing hypothesis on the etiology of IACCIs that has informed long COVID research is viral persistence—the idea that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins and/or RNA may drive long COVID symptoms. Studies have found viral proteins or RNA in numerous organ systems, which may indicate reservoirs of persistently replicating virus in people with long COVID.[5] Several clinical trials are now underway to test if extended courses of the antiviral nirmatrelvir/ritonavir (Paxlovid) may help patients with long COVID, but given delays in implementation and research dissemination, some patients embarked on autonomous self-experimentation. One patient-led paper detailed a case series of 13 responses to the drug.[6] Using a patient-centered approach, this paper systematically documented experiences that had otherwise only been shared informally and allowed for more insights than available in health records, revealing nuanced data on how extended courses of nirmatrelvir/ritonavir may help some symptoms for some patients but not others.[6] The Patient-Led Research Fund, a patient-led participatory grant-making fund, is also funding one of the first trials targeting viral persistence with monoclonal antibodies.

Another important direction of patient-led research involves the gut microbiome and immune dysregulation. Both patient-led research projects and clinical trials[7] have shown promise in alleviating neurological long COVID symptoms by altering the microbiome. These findings implicate the gut microbiome as a mediator of symptoms such as brain fog and cognitive dysfunction, which are linked to neuroinflammation and immune dysfunction in long COVID. Immune dysregulation in long COVID may also contribute to vascular damage, microclots, hypercoagulability, and thromboembolic states. Work supported by the Patient-Led Research Fund explores these hypotheses as well as the nature of immune dysregulation in long COVID, the potential of treating hypercoagulable states with anticoagulants, the pathophysiology of PEM, and more and has yielded some of the most meaningful findings in long COVID, including on mechanisms of PEM[8] and T cell exhaustion.[9] This vital research may lead to much-needed biomarkers and diagnostic tools and also presents potential targets for long COVID treatments.

In addition to directly conducting and funding long COVID research, patients act in advisory capacities to improve long COVID research efforts. Examples where patient representatives were meaningfully engaged throughout the entire research process—from determining research priorities and generating hypotheses through study design, analysis, and publication—include National Clinical Cohort Collective (N3C)'s large-scale studies with electronic health record data, the FDA CURE-ID's critical endeavor to identify repurposed drugs, an assessment of long COVID healthcare needs in Brazil, a study on episodic disability, and multiple clinical trials. Patients were also central to the National Academies of Science, Engineering, and Medicine (NASEM) definition of long COVID and in creating the Centers for Disease Control and Prevention's guidelines for the condition, as well as in advocacy initiatives seeking to increase research funding and social support programs for those with long COVID. Patients additionally help provide medical education worldwide, presenting at webinars run by the World Health Organization, National Institutes of Health, medical schools and societies, global non-governmental organizations (NGOs), and others.

Resolving disconnects between long COVID patients and researchers

Understanding the disconnects

Despite the progress that has been made, we do not yet comprehensively understand the etiology of long COVID—or even whether there is a single unifying pathological change driving symptoms or if there are heterogeneous causes. COVID-19 infections can damage multiple organs and organ systems, even in patients who were considered low risk.[4] Long COVID symptoms manifest in diverse ways for different patients and have the potential to affect every organ system. Some studies have focused on one organ system (e.g., pulmonary, cardiovascular, gastrointestinal), one organ (e.g., lungs, kidneys, liver), one set of symptoms (e.g., orthostatic intolerance), or one type of patient inclusion criteria (e.g., hospitalized patients). Results generated without consideration of heterogeneous presentations of long COVID face real risk of not generalizing across patient populations.

As patient-researchers, we have also had to spend considerable time and resources refuting the framing of long COVID as psychological, psychosomatic, or due to deconditioning. These framings alienate patients and allocate precious limited resources to dead-end hypotheses rather than evidence-backed scientific trials. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have historically been implemented in combination in attempts to treat ME based on the hypothesis that the etiology of ME is principally psychological and symptoms are due to deconditioning. However, considerable evidence has shown that GET and CBT either individually or in combination do not improve symptoms of ME; indeed, these treatments can actually cause direct harm to patients through exacerbation of PEM.[10] In addition, the insistence that the pulmonary, renal, cardiovascular, neurocognitive, rheumatological, olfactory, autonomic, and other manifestations of long COVID are due in whole or in large part to psychological dysfunction engenders tremendous mistrust in long COVID researchers and care providers. The fallacious framing of long COVID as a psychosomatic disease can furthermore create immense barriers for researchers and clinicians who *are* well-informed and conducting meaningful research because they must simultaneously cope with patient mistrust and peer skepticism. Although accessing competent mental healthcare or alternative therapies such as meditation can help to cope with any chronic illness and improve outcomes, these are complementary approaches and not cures for long COVID, IACCIs, autoimmune diseases, or other associated conditions, including neurovascular diseases.

Better understanding of neurovascular dysfunction and manifestations of neuroinflammation in long COVID and IACCIs is needed to help identify treatments, including immunotherapies and/or regenerative medicine. Patients often identify this as a high priority, given the debilitating

nature of neurologic symptoms like severe fatigue and cognitive impairment (often referred to colloquially as brain fog). However, neuroinflammation and microscopic changes to brain capillary perfusion are difficult to capture in living subjects. Studies to date in brains of postmortem subjects have shown vascular damage[11] and viral perseverance months after a COVID infection,[12] but cohorts in these postmortem studies may not be representative of demographics affected by long COVID since they have focused on the elderly, the immune-suppressed, those who died in hospital with acute COVID, and those who died shortly following infection. Creating a brain and tissue bank of diverse people with long COVID and IACCIs would support studies to better understand cellular changes driving the symptoms of these diseases. This may also yield better humanized models of long COVID and IACCI pathogenesis that can be used for therapeutic screening—a necessary stepping stone toward the development of treatments and cures for these conditions.

Bridging the gap: Effective strategies

Research on long COVID must account for the specific needs of long COVID patients. In designing both clinical and basic research studies on long COVID in human subjects, too few researchers consider the effects of study participation on patients' health. Traveling to and from study sites, filling out extensive questionnaires, and otherwise participating in research can exacerbate PEM and other long COVID symptoms. Studies should be designed to protect patient welfare while ensuring inclusion of patients with varying severities of the illness, especially because house- and bed-bound patients have paradoxically often been excluded from IACCI research, even though their conditions are the most dire. Examples of accommodations include enabling patients to participate remotely and at their convenience whenever possible, allowing surveys to be completed online, mailing study interventions, and conducting in-home visits. Participation options of telephone calls and SMS messaging add convenience and trust particularly for those without broadband access, an issue that is disproportionately likely to affect minority populations in the US and economically disadvantaged households worldwide. When on-site interactions are needed, all present should wear N95 masks and air should be filtered within parameters that reduce the risk of COVID reinfections as well as suprainfections. Many patients are likely to need accommodations such as areas to recline and rest in quiet before and after in-clinic visits.

Long COVID researchers must carefully consider inclusion and exclusion criteria. One specific consideration that can lead to selection biases is reliance on a positive PCR test for inclusion. Whether for clinical trials, basic research studies, or analyses of electronic health records, clinical diagnoses of COVID and/or long COVID are more reliable in identifying people with the condition because testing is neither equitably available nor equitably sought. Access barriers include test costs for the uninsured, strictly triaged PCR tests during peaks of COVID transmission, and denial of access to COVID testing, particularly for those who were seen as at lower risk for complications of acute infection, such as children. The rise of at-home tests has additionally decreased the use of PCR testing, though at-home antigen tests and the more-sensitive nucleic acid amplification tests (NAATs) are not always widely accessible or covered by insurance. Furthermore, a negative COVID test should not define control groups because false negativity is a significant confounder, especially for women and children, and particularly if testing occurred early in the course of symptoms.[13] Additionally, groups prioritized for PCR testing during transmission peaks have more significant comorbidities, and this will bias measures of health outcomes in control populations defined by negative PCR tests. Seropositivity/seronegativity likewise are unreliable indicators of infection history: some do not generate antibodies in response to infection, while others serorevert; women are disproportionately likely to serorevert.[14]

Designing the research that long COVID patients need: Clinical trials of potential treatments

Patient priorities: A drug discovery pipeline alongside trials of repurposed drugs and therapeutics

Patients' first priority is well-designed clinical trials of potentially curative therapies, with a second priority of trialing treatments to improve symptoms.[15] The urgency and energy with which global governments, research, and clinical communities collectively mobilized to develop treatments and vaccines for acute COVID should be applied to respond to the expansive public health crisis of long COVID. The long COVID clinical trials that currently exist are not commensurate with the urgent need for approved treatments or the burden and prevalence of long COVID. Most of the 351 interventional clinical trials on ClinicalTrials.gov as of April 17, 2024, test non-pharmaceutical interventions or lack the rigor required to demonstrate the effectiveness of the interventions being tested.[15]

Research identifying physiological differences between those with and without long COVID can lead to treatment targets, some of which may have existing drugs that can be repurposed.[4] The main barrier to clinical trials of repurposed drugs is adequate public funding. Because there is little financial incentive for pharmaceutical companies to investigate off-patent medications, public funding is necessary for well-controlled, multi-arm clinical trials that account for the heterogeneity of long COVID and have clinically relevant outcome measures. Randomized control trials are needed to determine what presentations of long COVID most benefit from specific interventions, including both pharmaceutical and non-pharmaceutical interventions.

However, because no drug currently on the market has been shown to be curative for long COVID or any other IACCI, substantial investments must also be made in the bench-to-bedside drug development pipeline. Basic research must be funded to better understand the pathobiology of long COVID, discover biomarkers and treatment targets, and develop *in vitro* and *in vivo* models that can be used to screen potential therapeutics. Strong pathobiological work must also be undertaken on the areas patients most care about and are most debilitated by, including research to understand the mechanisms behind PEM and potential viral reservoirs.

As a secondary priority, clinical trials on non-curative treatments that may reduce symptom burden could benefit many patients. There is abundant anecdotal

evidence from patients that experimental uses of certain pharmacological (e.g., ivabradine, low-dose naltrexone) and non-pharmacological (e.g., hyperbaric oxygen therapy, acupuncture, stellate ganglion block, vagus nerve stimulation, transcranial direct stimulation) interventions can improve both symptoms and daily function in some patients; however, these unproven modalities remain prohibitively expensive and impossible to access for the majority of people with long COVID. Clinical trials of these types of interventions could increase access and pave the way for insurer and public-payer approval, easing symptom burden as we await curative care.

Effective clinical trial design

Because biomarkers for long COVID have not yet been validated for clinical use, we recommend using symptom-based assessments (e.g., Cogstate or CNS Vital Signs, SBQ-LC, COMPASS-31) and quality-of-life assessments (e.g., FUNCAP, SF-36) to measure clinical trial outcomes. Symptom-based metrics allow for the detection of isolated effects while quality-of-life metrics can detect increased capabilities. Patients often adapt their level of exertion to decrease symptom severity (i.e., using pacing), so capability-based metrics can reveal an intervention's true effect on the patient's health status. Special considerations must be in place for pediatric patients when developing and utilizing survey instruments—long COVID symptoms can manifest differently in children and adolescents, and the youngest patients with long COVID may lack the vocabulary to describe what they are experiencing.

In addition, clinical trials must thoughtfully consider whether to include participants with other IACCIs and/or IACCIs that preceded COVID infections. Inclusion of these conditions will enable comparisons between conditions that could enable each trial to benefit larger populations and improve understanding of which treatments are helpful for IACCIs that arise from pathogens beyond COVID, as well as the impact of COVID infections and reinfections on people with IACCIs.

Addressing patient priorities

Achieving what is needed to solve long COVID and all IACCIs requires meaningful engagement of patients in research; diverse, representative, and global studies; and significant governmental and private investment worldwide. Patient-led and patient-driven research in long COVID and IACCIs has already led to more relevant and less biased research. Patient-researchers *are* researchers. Our inclusion cannot be seen as tokenism but rather as an essential way to define research priorities and develop well-informed hypotheses, rigorous study design, and efficient allocation of funding. These ideas come from a long history of patient-driven and community-engaged research in other disease spaces, from rare diseases to HIV/AIDS, and these learnings can and should be applied throughout the biomedical research field.

Throughout the entire span of a translational research project, studies must center insights that can only be learned through the lived experiences of patients. This requires active patient engagement, starting from the study concept phase through data analysis and dissemination, and ensuring there are opportunities throughout to change study directions in response to feedback. It is particularly important to consider power dynamics between academic researchers and patients and how to subvert historical hierarchies to ensure that patients have meaningful power in research decision-making. Patients who are reflective of the diversity of the long COVID community need to be involved in co-developing research questions and methodologies. Research findings must also be communicated in ways that are rapid, relevant, and rigorous to patient communities. This community-engaged approach can improve data collection and quality and make scientific research more rigorous. We recommend that research teams use resources such as the scorecards created by PLRC and the Council of Medical Specialty Societies to guide and evaluate their engagement of patients in research. We encourage funders to involve patients in funding decisions. The Patient-Centered Outcomes Research Institute is one example of a funder that prioritizes patient engagement in research. Not all researchers know best practices for patient engagement in research; we encourage those researchers to partner with those who do (including those with experience in patient-led research, community-based participatory research, and Indigenous data sovereignty research). We also encourage degree programs that prepare future health researchers to include such content in their required coursework

We encourage studies to include entire patient populations, including those with severe illness, pediatrics, low-income households, people of diverse genders, people living in undersampled geographical locations including rural areas and across low- to middle-income countries (LMICs), and Black, Indigenous, and People of Color (BIPOC) individuals. The challenges around recruitment of diverse populations inherent to all human-subject research are pronounced in long COVID research, and the result is that the populations most impacted by the illness are often not representatively studied. A lack of Black scientists and racial/ethnic, gender, and disability diversity in the pool of academic researchers also contributes to institutional shut-out and mistrust. Awareness of these issues can help mitigate their effects. Inclusion of participants from marginalized communities as active collaborators, rather than only as subjects of research, can ensure that communities most impacted by long COVID are at the table as valued partners.

Moreover, while long COVID is a global problem, the impact of long COVID is not evenly distributed across the world. Studies in LMICs that engage local patient communities are needed to understand priorities for patients outside high-income nations and to contextualize LMIC-centered agendas. Clinical trials should aim for cross-country recruitment wherever possible and utilize participatory action research principles and a fair-benefit framework.

Despite the prevalence of long COVID, the condition remains underdiagnosed, perhaps due to lack of physician knowledge and awareness of diagnostic criteria and International Classification of Diseases (ICD) codes. Failure to recognize and diagnose long COVID poses a risk to patient trust and may also pose a risk to patient safety if disproven modalities such as GET are prescribed. Engaging physicians, particularly general practitioners, in long COVID research can help build a common understanding of long COVID at the point of care. NASEM's definition of long COVID should be followed up with clinician education

programs by professional organizations (such as the American Medical Association) in order to achieve appropriate diagnostics in clinical practice. Formal diagnosis can allow for better coordinated care, patient education, research participation, and access to disability benefits. Improved clinical recognition of long COVID will also lead to better estimates of the degree of mortality associated with the condition.

The clear scientific consensus—that long COVID is a real, biologically driven, and often disabling illness that continues to threaten the public's health—"diverges from concurrently developing collective representations of the pandemic," which falsely present the COVID-19 pandemic as being in the past tense and the outcomes of the COVID-19 pandemic in purely psychological terms. This framing results in many people, including some clinical care providers, psychologically distancing themselves from acknowledging the risks a SARS-CoV-2 infection poses to themselves and their families. In the healthcare setting, the framework of COVID as past tense creates underdiagnosis of long COVID, puts vulnerable patients at risk of re-infection, and engenders mistrust; globally, it puts long COVID research funding and support in jeopardy and increases the societal burden of long COVID.

Overcoming long COVID together

Success in the vital mission to overcome long COVID requires significant investment and resources. Long COVID cannot be a politicized condition—research funding must be allocated regardless of political environment. Ensuring sustained funding is important for research continuity and to minimize churn of researchers in the field. We emphasize the power of government and private funders to incentivize many of the recommended shifts in long COVID research by how they award funds. For example, we recommend that funders (1) put out specific calls for proposals to fund clinical trials of potentially curative long COVID treatments that build upon the most up-to-date science; (2) require patient review of proposals to ensure grants align with patient priorities and that studies are rigorously designed and patient-centered (as was done with the Patient-Led Research Fund); (3) support studies that involve patients in the study concept, design, review, and publication process; (4) require that applicants include meaningful engagement of patients throughout their research process; and (5) require that cohorts reflect the diversity of the patient community. Even if not specifically requested by a funder, we encourage researchers to design studies that meet these criteria. Additionally, funders should invest in early- and mid-career researchers and medical education to catalyze new generations of IACCI research. Funders can ensure expertise on projects by prioritizing grants for scientists who have lived experience of long COVID or an IACCI as a patient or caregiver while stipulating that work accommodations are available (e.g., remote work, flexible hours, paid sick leave, ventilation and other COVID risk mitigation measures for in-person work, and mobility supports as applicable). Academic journals can reinforce these calls for patient engagement by requiring a description of patient and/or community engagement in the study and involving patients as peer reviewers.

Long COVID research must be informed by patients' lived experiences to ensure relevant and scientifically robust findings. Our best chance to solve the growing long COVID health and economic crises lies in creating purposeful synergy between researchers, funders, decision makers, and patients.

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DECLARATION OF INTERESTS

The authors have no competing interests to declare.

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